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17-Hydroxyprogesterone in premature infants as a marker of intrauterine stress

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Abstract: AIMS: Amniotic infection (AI) and preeclampsia (PE), which are commonly the reason for prematurity, inflict stress of different duration on immature fetuses. Whether chronic stress, as reflected by intrauterine growth retardation, influences the level of 17-OH progesterone (17-OHP), was not previously examined. **METHODS:** We analyzed 17-OHP and TSH levels during neonatal screenings in the first hours of life of 90 premature infants born between 25 and 33 weeks of gestation in infants with AI (n=37) or with PE (n=53). Control of acute stress parameters was derived from umbilical arterial cord blood pH and base excess (BE). **RESULTS:** Mean 17-OHP levels of infants born to mothers with PE were 85.7 nmol/L compared to 54.6 nmol/L ($P<0.001$) in AI infants. 17-OHP was even higher when intrauterine growth restriction was present (99.8 nmol/L). Antenatal steroids and mode of delivery did not significantly affect 17-OHP levels. **CONCLUSIONS:** Stress of relatively long duration, as in cases of PE, leads to a significant increase of 17-OHP level in preterm infants. The postnatal 17-OHP level may be considered as a measure for severity of intrauterine stress and might be used as an individualized indicator for earlier intensive care.

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17-Hydroxyprogesterone in premature infants as a marker of intrauterine stress

Jörg Ersch¹, Ernst Beinder², Thomas Stallmach^{3,*}, Hans Ulrich Bucher¹ and Toni Torresani⁴

¹ Department of Neonatology, Zurich University, Switzerland

² Department of Obstetrics and Gynecology, Zurich University, Switzerland

³ Department of Pediatric and Developmental Pathology, Division of Pathology, Zurich University, Switzerland

⁴ Children's Hospital, Zurich University, Switzerland

Abstract

Aims: Amniotic infection (AI) and preeclampsia (PE), which are commonly the reason for prematurity, inflict stress of different duration on immature fetuses. Whether chronic stress, as reflected by intrauterine growth retardation, influences the level of 17-OH progesterone (17-OHP), was not previously examined.

Methods: We analyzed 17-OHP and TSH levels during neonatal screenings in the first hours of life of 90 premature infants born between 25 and 33 weeks of gestation in infants with AI (n=37) or with PE (n=53). Control of acute stress parameters was derived from umbilical arterial cord blood pH and base excess (BE).

Results: Mean 17-OHP levels of infants born to mothers with PE were 85.7 nmol/L compared to 54.6 nmol/L ($P < 0.001$) in AI infants. 17-OHP was even higher when intrauterine growth restriction was present (99.8 nmol/L). Antenatal steroids and mode of delivery did not significantly affect 17-OHP levels.

Conclusions: Stress of relatively long duration, as in cases of PE, leads to a significant increase of 17-OHP level in preterm infants. The postnatal 17-OHP level may be considered as a measure for severity of intrauterine stress and might be used as an individualized indicator for earlier intensive care.

Keywords: Amniotic infection; 17-hydroxyprogesterone, intrauterine stress; preeclampsia; prematurity.

*Corresponding author:
Prof. Dr. T. Stallmach, MD
Department of Pathology
University Hospital Zürich
Schmelzbergstr. 12
CH-8091 Zurich
Switzerland
Tel.: +41 44 255 2101
Fax: +41 44 255 2883
E-mail: thomas.stallmach@usz.ch

Introduction

In 1992, Switzerland introduced a screening test for congenital adrenal hyperplasia based on the 17-hydroxyprogesterone (17-OHP) level in neonatal blood. Physiological 17-OHP values for the days and weeks after birth are thus well defined [11, 18, 21, 28]. Initial levels in preterm infants are much higher than in term infants, but this does not necessarily indicate congenital adrenal hyperplasia. Rather, it appears that intrauterine stress stimulates fetal steroid synthesis by activating the hypothalamic-pituitary-adrenocortical axis. Elevated postnatal cortisol levels are characteristic of infants born prematurely after amniotic infection (AI) or preeclampsia (PE) [2, 6, 9, 10, 12, 22]. As a precursor of the cortisol pathway 17-OHP could thus serve as a marker of intrauterine stress.

In developed countries the incidence of preterm birth varies between 5 and 10% [32] and divides into two large and relatively homogeneous groups. AI due to the access of bacteria to the amniotic fluid and, by extension to the placenta, causes relatively brief fetal stress because in most cases premature birth soon follows. Such fetuses are usually found to be well nourished. Autopsy studies have shown some adaptation to infectious stress as the fetus can exhibit a granulopoietic response [13, 24] and form bronchus-associated lymphoid tissue as a specific reaction to AI [5]. PE, on the other hand, causes prolonged fetal stress resulting in infants who appear starved when eventually born prematurely after labor induction or cesarean section performed for maternal indications [14, 25, 26].

The aim of the present study was to characterize and compare 17-OHP levels in prematurity associated with AI and PE, based on the hypothesis that 17-OHP levels would be lower in the AI group.

Patients and methods

The study population comprised 90 premature infants born between 25 and 33 weeks' gestation (Table 1). Infants with malformations or chromosomal abnormalities were not included. Of the 37 AI infants, 20 were born between 1993 and 1999 and had been included in a previous study [4]; the additional 17, who met the same four diagnostic criteria (maternal fever, elevated maternal C-reactive protein, fetal tachycardia, and chorioamnionitis on placental histology), were born between January 2003 and November 2004. There were no changes in biochemical analytical methods between periods. Similarly, of the 53 PE infants, 25 were born between 1993 and 1999 and had been

Table 1 Gestational age of 90 infants exposed to amniotic infection or preeclampsia.

	n	Mean	Median	Range
Amniotic infection	37	28 5/7	28 3/7	25–33
Preeclampsia	53	29 4/7	29 6/7	24–33

included in the previous study [4]; the additional 28, whose mothers met the same diagnostic criteria (proteinuria >300 mg/d, and diastolic blood pressure >90 mm Hg on two occasions at least 4 h apart, after week 20 of gestation and regressing after delivery) [19], were born between January 2003 and November 2004. Intrauterine growth restriction (IUGR) was suspected when estimated fetal weight was below the 5th percentile of the reference chart in combination with either pathological umbilical artery Doppler blood flow or a diminished amount of amniotic fluid. However, for this study only actual birth weight <10th percentile was used (n=20, all in the PE group). Infants with AI were born either by cesarean section (25 infants) or spontaneously (12 infants), whereas infants from the PE group were all born by cesarean section. Antenatal steroids were given to the 33 of 53 infants from the PE group and 34 of 37 infants with AI.

In order to control for acute stress, the umbilical arterial cord blood gas analysis and the 1-min Apgar score of all premature infants were evaluated and compared (Table 2).

Blood was collected onto filter paper (dried blood spots [DBS] technique) in the first three hours of life from the umbilical artery catheter placed in all infants weighing <1000 g or with actual or imminent respiratory decompensation. 17-OHP levels were measured with a solid-phase competitive fluoroimmunoassay using europium (Eu) labeled 17-OHP as tracer (Delfia neonatal 17-OHP kit, Wallac, Turku, Finland). DBS disks three millimeters in diameter were punched into microtiter plate wells coated with anti-mouse IgG. Assay buffer and 17-OHP antibody were added to the wells and incubated under shaking for one hour; Eu-labeled 17-OHP was then added, followed by incubation for two more hours under shaking. After washing to remove non-reacted components, Eu fluorescence was read with a time-resolved fluorometer, and 17-OHP results expressed as nmol/L blood. All assays were performed in duplicate. Thyroid-stimulating hormone (TSH) was measured using a sandwich fluoroimmuno-

Table 2 Stress indicators: Mean umbilical artery pH, base excess and 1-min Apgar score in 90 premature infants exposed to amniotic infection or preeclampsia.

	pH	Base excess	Apgar
Amniotic infection	7.31	−2.8	5
Preeclampsia	7.27	−2.2	5

Table 3 Thyroid-stimulating hormone (TSH) and 17-hydroxyprogesterone (17-OHP) in 90 infants exposed to amniotic infection or preeclampsia.

	TSH (mU/L blood)		17-OHP (nmol/L blood)		17-OHP >55 nmol/L blood	
	Mean	Range	Mean	Range	n	%
Amniotic infection	12.7	2.3–43.4	54.6	21.5–164	16	43
Preeclampsia	10.0	1.3–28.4	85.7	26.1–293	39	74

assay (Delfia). Punched three millimeter DBS disks were incubated with buffer and Eu-labeled TSH in microtiter plates for four hours under shaking. Fluorescence was measured after washing and TSH results expressed as mU/L blood.

The Mann-Whitney non-parametric test was used to compare unpaired groups followed by a χ^2 test for nominal data at the 5% significance level.

Results

Acute stress parameters – umbilical artery pH, base excess and 1-min Apgar score – did not differ significantly between the groups (Table 2). Birth weight, a chronic intrauterine stress parameter, was lower in infants from the PE group ($P<0.01$). 17-OHP levels were unrelated to gestational age within the range of our population (25–33 weeks). The intergroup difference in mean 17-OHP levels was highly significant: 54.6 nmol/L in the AI vs. 85.7 nmol/L in the PE group ($P<0.001$), and was even more striking – 54.6 nmol/L vs. 99.8 nmol/L – if intrauterine growth restriction (birth weight <10th percentile: n=20, all in the PE group) was present. In addition, values above the 50th percentile of the normal value for premature infants (55 nmol/L blood) [28] were more frequent in the PE group (74% vs. 43%, Table 3), indicating that the “normal” range is skewed by the inclusion of pathological conditions of infants at birth. In contrast to 17-OHP, TSH levels (AI: 12.7 mU/L; PE: 10.0 mU/L; PE + birth weight <10th percentile: 10.9 mU/L blood) did not differ significantly between the groups (Table 3).

Antenatal steroids did not significantly affect 17-OHP (in the AI group: mean value with antenatal steroids was 55 nmol/L compared to 47 nmol/L in cases without steroids, $P=0.63$; in the PE group: mean value with antenatal steroids was 76 nmol/L compared to 92 nmol/L in cases without steroids, $P=0.10$). Regarding mode of delivery, AI only could be studied. 17-OHP was not significantly different between subgroups (mean value after cesarean 56 nmol/L vs. mean value after spontaneous delivery 50 nmol/L).

Discussion

Neonatal screening comprises, among others, 17-OHP and TSH assessment [3, 11, 16, 18, 21, 28]. Low serum TSH values have been reported in prematurity associated

with PE or placental insufficiency [7]. Our sample confirmed lower TSH values in the PE group but the difference was not significant. In contrast, the difference in 17-OHP levels between AI and PE infants was highly significant, with levels being even more increased in growth-restricted infants from the PE group. In accordance with Gatelais et al. [8] this was not influenced by a single course of antenatal steroids.

We draw the following conclusions: (i) raised 17-OHP levels can be used as a marker of chronic intrauterine stress, in contrast to cortisol which is increased under a variety of conditions [2, 6, 9, 15, 22]; (ii) the wide variance in "normal" prematurity 17-OHP is most probably due to the failure, when setting the normal range, to exclude growth-restricted infants of PE pregnancies, a common prematurity subgroup [3, 11, 16, 18, 21, 28]; our data indicate that normal 17-OHP levels need to be redefined given that maternal PE accounts for about 30% of all preterm infants, not only in our sample but also in others [23, 27]; (iii) high 17-OHP levels in individual infants signify greater risk and earlier requirement for intensive care [1, 4, 12, 17, 20, 29–31].

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